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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/030,752	04/03/2002	Dominique Caille	SYL 550	2032

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EXAMINER	
KWON, BRIAN YONG S	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 06/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/030,752	CAILLE, DOMINIQUE	
	Examiner	Art Unit	
	Brian S Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12152003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Summary of Action

I. The objection to the specification is not maintained in light of the amendment.

II. The objection to the claim 6 is not maintained in light of the amendment.

III. The rejection of claims 1-6 under 35 USC 101 is not be maintained in light of the amendment.

IV. The rejection of claims 2-3 and 5-6 under 35 USC 112, second paragraph, is maintained for the reason of the record.

V. Applicant's amendment necessitates a new ground of the rejection(s) in this Office Action.

Status of Application

1. By an amendment filed December 15 2003, Claims 1-6 have been amended and Claims 7-12 have been newly added. Claims 1-12 are currently pending for prosecution on merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of "diabetic neuropathies, polyarthritis, arthrosis, lumbago and traumatological pain", does not reasonably provide enablement for treatment of

"inflammation", "the symptomatic treatment of painful conditions of light to moderate intensity and/or feverish states" and "inflammation in the ENT field". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

All rejected claims are drawn to the methods of treating inflammation damage in patients with the administration of the instant composition.

(2) The state of the prior art

There are no known compounds of similar structure which have been demonstrated to treat all types of inflammatory diseases or conditions. For instance, many types of cancers (e.g., bladder, colon, pancreas, stomach, etc...) are characterized by inflammation. Cecil Textbook of Medicine states that "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different method of growth and harm

to the body. Also see In re Buiting, 163 USPQ 689 (CCPA 1969), wherein 'evidence involving a single compound ant two types of cancer, was held insufficient to establish the utility of the claims directed to disparate of cancers'. Thus, it is beyond the skill of oncologists/clinicians today to get an agent to be effective against all types of cancers and/or inflammatory diseases in general. Since applicant's assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "silver bullet" is contrary to our present understanding of oncology.

(3) The relative skill of those in the art

The relative skill of those in the art of pharmaceuticals is high.

(4) The predictability or unpredictability of the art

The unpredictability of the pharmaceutical art is very high. Applicant has not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds for accomplishing the desired result of the claimed invention without undue amount of experimentation. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See In re fischer, 427 F.2d 833, 839, 166 USPQ 10, 24(CCPA 1970).

(5) The breadth of the claims

The claims are very broad. The breadth of the claims not only includes the disclosed examples of diabetic neuropathies, polyarthritis, arthrosis, lumbago and traumatological pain, but also pancreatitis, ALS, Alzheimer's disease, cachexia/anorexia, asthma, diabetes, glomerulonephritis, graft versus host rejection, hemohorragic shock, hyperalgesia, inflammatory

bowel disease, cancers (e.g., mouth cancer, esophageal cancer, lip cancer, colorectal cancer, brain cancer, liver cancer, etc...), psoriasis, contact dermatitis, atopic eczema, reperfusion injury, septic shock, multiple sclerosis, cerebral ischemia, bursitis, allergic neuritis, etc....

(6) The amount of direction or guidance presented or (7) The presence or absence of working examples

The specification discloses the use of succinic acid derivatives represented by the formula as an agent that is useful for the treatment of inflammation. As the specific embodiment of the claimed invention, (s)-2-benzyl-3-(cis-hexahydro-2-isoindolinylcarbonyl)propionic acid was tested in an experimental model of plantar inflammation in rats, and found to exhibit anti-inflammatory (page 3, line 20 thru page 5, line 12).

However, there is no demonstrated correlation that the tests and results apply to all of the disorders or disease conditions embraced by the instant claims. The specification fails to provide sufficient information allowing the skilled artisan to envision the desired result of the claimed invention without undue amount of experimentation.

(8) The quantity of experimentation necessary

The quantity of experimentation needed to be performed by one skilled in the art is yet another factor involved in the determining whether "undue experimentation" is required to make and use the instant invention. "the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." In re Wands, 858 F.2d 737, 8 USPQ2d 1404 (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 218 (CCPA 1976)). For these reasons, one of ordinary skill in the

art would be burdened with undue "painstaking experimentation study" to determine all of "inflammation", "the symptomatic treatment of painful conditions of light to moderate intensity and/or feverish states" and "inflammation in the ENT field" that would enabled in this specification.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 2-3 and 5-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Dependent claims 2-3 limit the independent claim 1 by reciting "the compound of formula (I) is compound...". The subgenus structures shown in claims 2-3 are depicted with (I) as the claimed structure in claim 1. The formula (I) structure shown in claim 1 differs from the structures in claim 2 and 3 labeled as the structure (I). This inconsistency in the claims makes the claimed subject matter vague and indefinite. Claims 5-6 are also rejected because they are depending on the rejected base claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Sato et al. (EP 0507534).

Sato teaches use of the claimed succinic acid derivatives represented by the formula (e.g., (s)-2-benzyl-3-(cis-hexahydro-2-isoindolinylcarbonyl)propionic acid) having hypoglycemic activity for the treatment of diabetes (abstract; Example 41) .

Since the broadly interpreted "inflammation" encompasses various disorders that are mediated or manifested by inflammation including diabetes, the reference anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. Claims 5-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sato et al. (EP 0507534) in view of NIH Publication No. 95-3185, 1995 ("Diabetic Neuropathy: The Nerve Damage of Diabetes").

The teaching of Sato has been discussed in above 35 USC 102(b) rejection.

NIH Publication No. 95-3185 teaches that the treatment of diabetic neuropathy aims to relieve discomfort and prevent further tissue damage. The reference discloses "the first step is to bring blood sugar under control by diet and oral drugs or insulin injections, if needed, and by careful monitoring of blood sugar levels...maintaining lower blood sugar levels helps reverse the pain or loss of sensation that neuropathy can cause. Good control of blood sugar many also help prevent or delay the onset of further problems".

The teaching of Sato differs from the claimed invention in the use of said compound of the formula such as (s)-2-benzyl-3-(cis-hexahydro-2-isoindolinylcarbonyl)propionic acid for "the symptomatic treatment of painful conditions of light to moderate intensity and/or feverish states", namely "treatment of diabetic neuropathies, polyarthritis, arthrosis, lumbago, traumatological pain and inflammation in the ENT field". To incorporate such teaching into the teaching of Sato, would have been obvious in view of NIH Publication No. 95-3185 that teaches the importance of maintaining lower blood glucose levels in treating or reversing symptoms of diabetic neuropathy (e.g., pain or loss of sensation) by oral hypoglycemic drug, diet or insulin injection.

One having ordinary skill in the art at the time of the invention was made would have expected that good control of blood glucose with the administration of oral hypoglycemic drug

would provide beneficial effect in the treatment of diabetic neuropathies or symptomatic treatment of painful conditions of light to moderate intensity. One having ordinary skill in the art would have expected that the administration of said compound having hypoglycemic activity is useful for the treatment or symptomatic treatment of painful conditions of light to moderate intensity, namely diabetic neuropathies. Therefore, one having ordinary skill in the art would have been motivated to make such modification, with the reasonable expectation of success, to extend the usage of said compound (e.g., (s)-2-benzyl-3-(cis-hexahydro-2-isoindolinylcarbonyl)propionic acid) to accommodate patient's preference and needs where the more effective treatment is desired. One would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

Conclusion

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be

calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached on (571) 272-0951. The fax number for this Group is (703) 872-9306.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Brian Kwon
Patent Examiner
AU 1614